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The application of formyl group activation of brompyrrole esters to a formal synthesis of lycogarubin C

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by

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I. Abstract

Lycogarubin C is a member of an interesting family of marine natural products, which contains two indole groups appended to a pyrrole scaffold at the 3 and 4 positions. Such compounds are proposed to be biosynthetically related to the important antitumor agent, Staurosporine[1]. Recent work in our lab involving the use of Suzuki cross-coupling reactions of an ortho activated bromoformylpyrrole ester has provided key intermediates for the synthesis of pyrrole natural products and pyrolle-based analogues.

II. Introduction

Our lab has recently shown a highly efficient and facile way to produce ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**4**), which is receptive to Suzuki cross-coupling at the 4 position with many aromatic boronic acids[2]. This is extremely important to the synthesis of functionalized pyrroles for several reasons. Firstly, **4** contains the pyrrole structure necessary for activating cross coupling, which has proved problematic when using non-activated bromopyrroles[3]. Secondly, the carbonyl at the 2-position is flexible enough to allow for variation in compounds made, since many transformations can be performed to the ethyl ester group. And finally, the present work in our lab indicates that a ketone group at the 5-position activates cross coupling, showing that the basic structure of **4** is versatile and has many useful routes for creating complex and highly functionalized pyrroles.

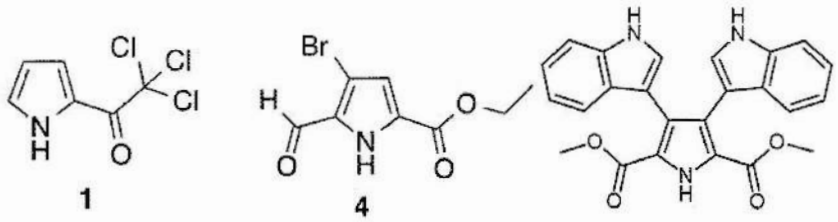


Figure 1. Key compounds: Trichloroacetyl pyrrole (**1**), bromoformylpyrrole ester (**4**), and lycogarubin C.

Setting lycogarubin C as our target tested several key aspects of **4** as a versatile pyrrole building block. Firstly, two N-sulfonylated indole boronic acids would need to be compatible with cross coupling at the 3- and 4-positions. This would test some of the scope of aromatic groups tolerated with the cross-coupling reaction. Secondly, **4** may allow us to

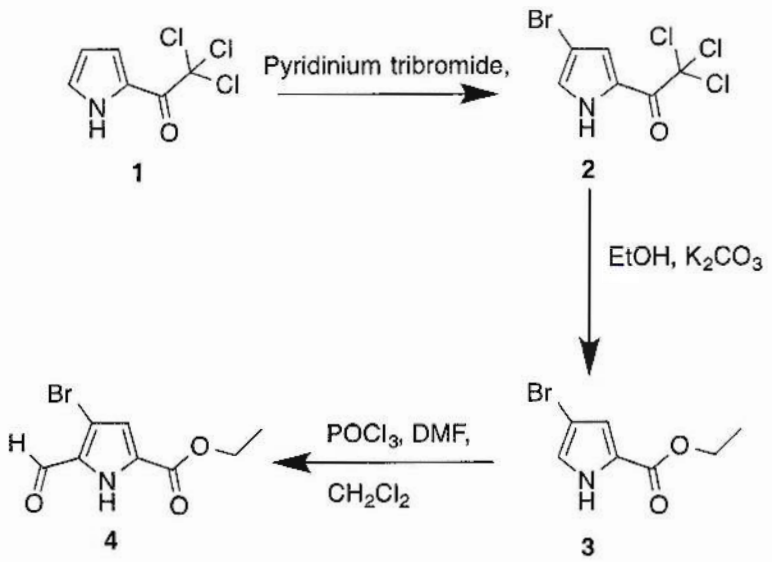
cross-couple independently at the 3- and 4- positions, which in the case of lycogarubin C, is not particularly important, but would still prove that stepwise addition of aromatic groups via cross-coupling to pyrroles is possible. Thirdly, the formal synthesis of lycogarubin C would reveal the possible scope of **1** as a building block to a library of pyrrole analogues that may provide interesting biological effects, as similar pyrrole natural products such as rebeccamycin and staurosporine have shown[4,5].

Members of the lycogallic acid family of molecules were first isolated in 1994 by Steglich[6] and Askawa[7] from the slime mold *Lycogala epidendrum*. Sherman et al.[8] further studied the enzymatic mechanism for rebeccamycin, a natural product structurally similar to lycogaruben C, and a molecule that has shown some anti-tumor properties in vitro[5]. Sherman's work showed that lycogallic acid was an intermediate in the production of rebeccamycin. To be able to produce lycogallic acid, and its homologue, lycogarubin C, could be extremely useful in efficiently building a library of pyrrole analogues. Since high-throughput screening and natural product discovery are two incredibly useful techniques in finding biologically active molecules, creating a large number of natural product analogues based in the lycogallic acid/lycogarubin C family is a useful method for potentially finding important molecules with interesting effects.

III. Results and Discussion:

Initially we attempted to produce lycogallic acid by starting with **4**. To produce **4**, we ran reactions as per previous results established[2]. Starting with 2-(trichloroacetyl)pyrrole, we ran a bromination using pyridinium tribromide as the brominating agent to add a bromine at the 4 position, followed by an esterification to

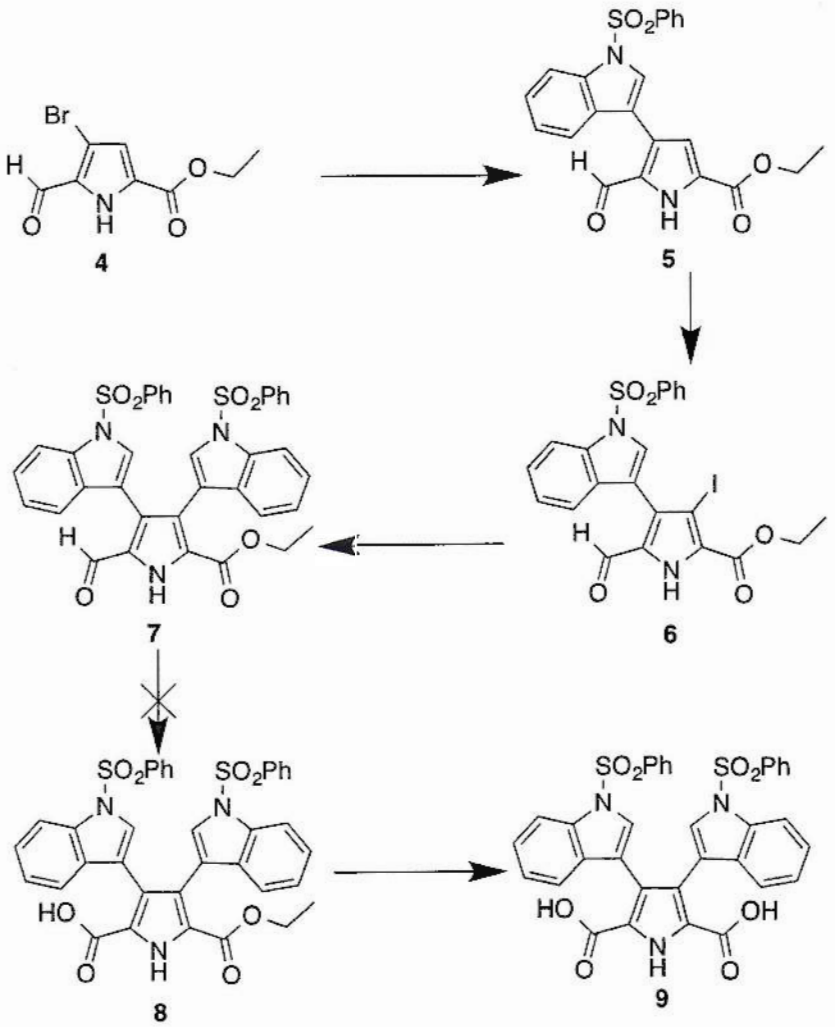
change the trichloro acetyl group to an ethyl ester. Next, to introduce an aldehyde group at the 5-position to activate cross-coupling, we ran a Vilsmeier-Haack reaction using $POCl_3$ and DMF in chloroform (scheme 1). At this point, we had a versatile intermediate capable of leading to many interesting pyrrole-based natural products.



Scheme 1. Preparation of flexible pyrrole intermediate.

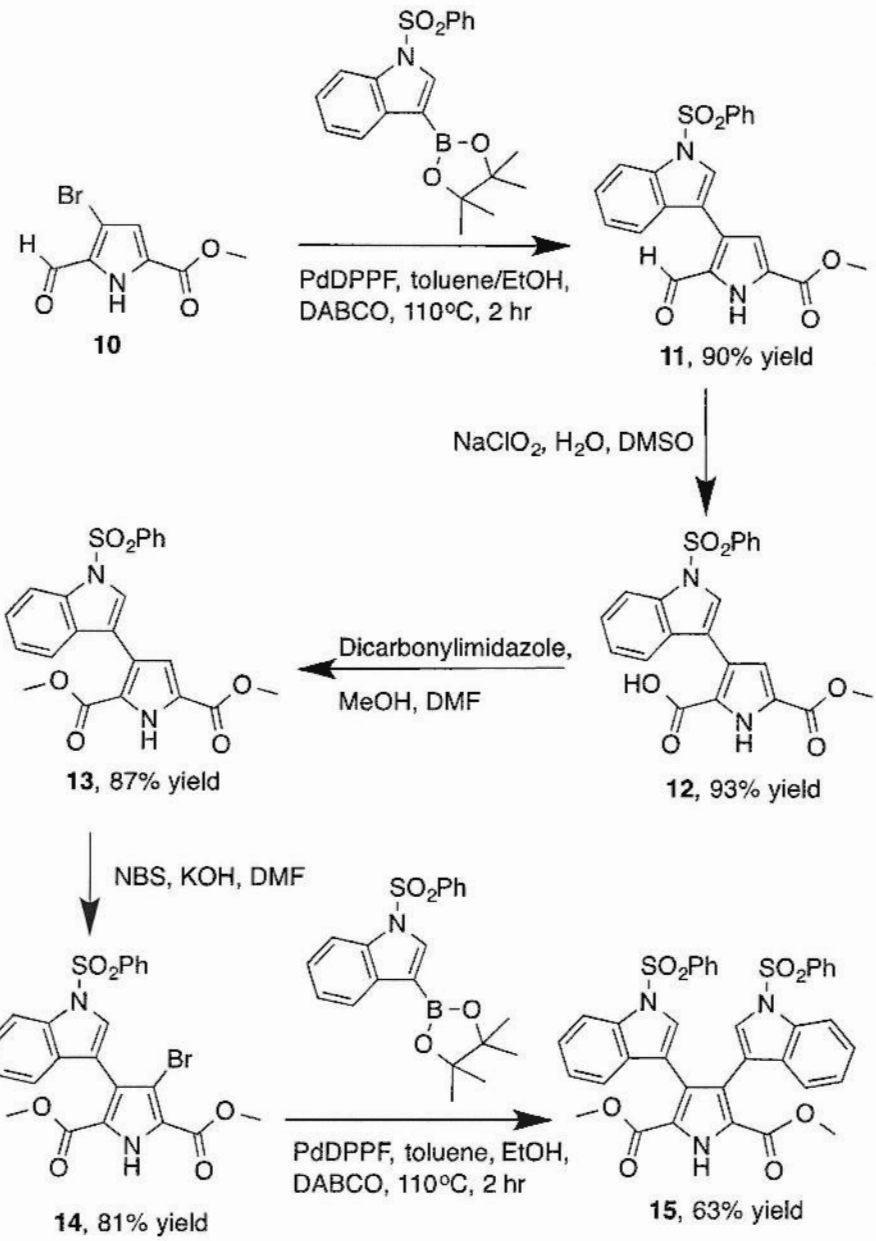
To prepare lycogallic acid, we proposed a Suzuki cross-coupling at the 4-position to add an N-sulfonylated indole, as per conditions outlined in our bromopyrrole ester paper[2]. We planned to iodinate at the 3 position, cross-couple there, then oxidize the aldehyde to a carboxylic acid, and then perform a hydrolysis of the ethyl ester to a carboxylic acid to complete the synthesis of lycogallic acid (scheme 2). This strategy was successful through the second cross coupling. However, the oxidation of the aldehyde resulted in only partial conversion to product, and the product and starting material were difficult to separate by column chromatography, leaving us with very low purified yields. Additionally, NMR

results were not completely conclusive that we had produced **8**, so we sought a different reaction scheme. We additionally attempted to hydrolyze the crude carboxylic acid pyrrole (**8**) to reach lycogallic acid, hoping that the NMR would become clearer, since lycogallic acid is a symmetrical molecule, thus making the NMR easier to discern. However, we did not produce enough (**9**) to successfully purify it using column chromatography.



Scheme 2. Proposed synthesis of lycogallic acid. We were unable to separate a mixture of products when oxidizing the aldehyde to a carboxylic acid.

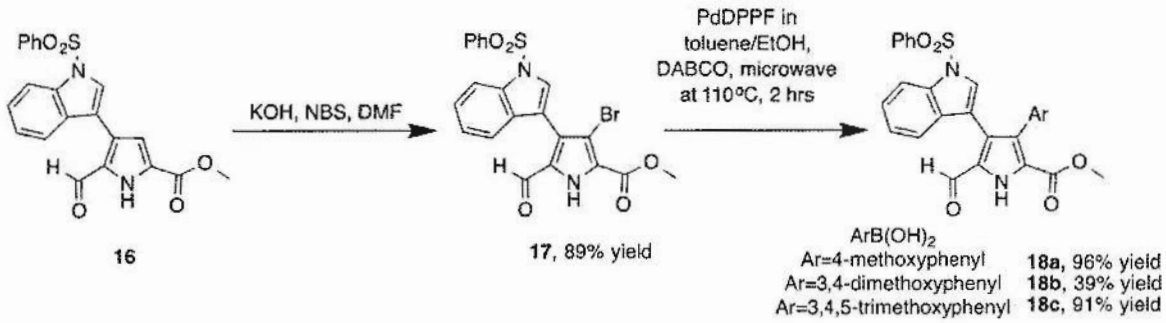
At this point we sought to prepare lycogarubin C instead, since its structure is similar to lycogallic acid, lycogarubin C is in the same family of molecules, and it involves many similar transformations as the lycogallic acid synthesis. Additionally, our synthesis of lycogarubin C would still show the flexibility of our bromoformylpyrrole ester intermediate. The Gribble and Boger[9,10] syntheses of lycogarubin C went through the *N,N*-sulfonylated intermediate, so we made this our goal to reach to complete a formal synthesis (scheme 3). We used methyl 3-bromo-formylpyrrole-5-carboxylate (similar to **4** but the methyl ester, not the ethyl ester) as our starting material from the three-step process we have published previously[2]. We then ran a Suzuki cross-coupling selectively at the 4-position to produce the mono cross-coupled product (**11**), which was to a carboxylic acid (**12**) using sodium chlorite in water and DMSO with excellent yield. The carboxylic acid pyrrole was then converted to a methyl ester (**13**) using carbonyldiimidazole and methanol through the formation of an intermediate carbonyl imidazole. We then brominated the 3 position using NBS and KOH in DMF. The brominated pyrrole (**14**) underwent a second Suzuki cross-coupling with N-sulfonylated indole boronic acid using the same conditions as the first cross-coupling to produce the Gribble intermediate to lycogarubin C (**15**). This reaction had a moderate (63%) yield, and we considered using iodine as the halogen to be replaced during cross-coupling, since iodinated molecules generally undergo cross-coupling more quickly than do brominated ones. However, we did not want to risk free radical halogenation or iodination in other positions on our starting material, nor did we want to lose product to decomposition since iodinated species can be unstable. Additionally, the bromination had excellent yields. To reach lycogarubin C itself, only a deprotection reaction removing the N-sulfonyl groups is necessary.



Scheme 3. Synthesis of Gribble precursor to lycogarubin C.

To further demonstrate the ability for the pyrrole ester to lead to highly functionalized pyrroles, we showed that other oxygenated aromatic boronic acids can undergo cross-coupling at the 3-position (scheme 4). We used these three boronic acids

because many pyrrole natural products are highly oxygenated in these positions, such as molecules in the rigidin family. While a rigorous scope of the aromatic groups was not investigated, we have shown that cross-coupling at the 4-position (which uses the same reaction conditions as at the 3-position) is tolerant to a large range of aromatic boronic acids and trifluoroborates, further showing the ability to quickly and efficiently produce a large library of lycogarubin C analogues.



Scheme 4. Synthesis of lycogarubin C analogues.

IV. Conclusions:

Our approach to the formal synthesis of lycogarubin C, as previously mentioned, accomplishes several important aspects that we sought. Firstly, our pyrrole building block is capable of leading to the formation of a lycogarubin C precursor in five steps (6 to reach lycogarubin C), proving that it is a useful intermediate for the preparation of complex and functionalized pyrrole natural products. Secondly, our synthesis adds aromatic groups in a stepwise fashion to the 3- and 4-positions of the pyrrole, which is not easily accomplished—previous syntheses of pyrrole natural products do not offer such liberty to make numerous analogues from a single intermediate. From **4** we have already shown that

numerous aromatic groups can be added to the 4-position[2], and in this work we show that several highly oxygenated aromatic groups can be added to the 3-position. These are simply examples of pyrrole-based analogues that can be made from our pyrrole building block.

To build upon the ability for our bromopyrrole ester building block, preliminary work in our group has shown that ketone groups at the 5-position, much like the aldehyde group in this work, also activate cross-coupling at the 4-position. This information allows us to more quickly prepare pyrrole-based natural product analogues, since rigidins A through E all contain benzoyl groups at the 5 position of the pyrrole (where we have the aldehyde in this work). Using this, we can create a plethora of rigidin analogues, showing that once again our bromopyrrole building block is an extremely useful intermediate for numerous pyrrole natural products.

V. Experimental Procedures:

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fischer scientific). All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were taken on either a Bruker 300 MHz or 500 MHz spectrometer in $CDCl_3$, DMSO-D_6, or D_6-acetone solutions. IR spectra were recorded on a Nicolet 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were obtained on a Shimadzu IT-TOF mass spectrometer at the University of Richmond. Low resultion GC-MS spectra were taken on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Chromatographic purifications were carried out on a Biotage SP-1 instrument or a Biotage Isolera instrument, both using a silica cartridge. Gradient elution with ethyl acetate/hexanes was used for both instruments. TLC analyses were conducted on silica plates with hexanes/ethyl acetate as the eluent. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity >95%.

All procedures taken from our 2014 publication in *Tetrahedron*, titled, "The application of formyl group activation of bromopyrrole esters to formal syntheses of lycogarubin C, permethyl storniamide and lamellarin G trimethyl ether".

Methyl 3-bromo-2-formylpyrrole-5-carboxylate (**10**). Into a 100 mL round bottom flask equipped with magnetic stirring and a rubber septum cap was placed 10 mL of anhydrous dichloromethane, 1.61 g (0.022 mol) of dry DMF, 2.90 g (0.019 mol) of phosphorus oxychloride and the resulting mixture was stirred in an ice bath for 10 min. To this flask was then added 1.28 g (0.0063 mol) of methyl 4-bromopyrrole-2-carboxylate in 10 mL of anhydrous dichloromethane and the resulting mixture was stirred overnight at room temperature. The reaction was worked up by the addition of 50 mL of water and separation of the two phases. The aqueous phase was extracted with additional dichloromethane

(3x15 mL) and the combined dichloromethane phases were washed with brine (1x15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield 1.20 g (82% yield) of a light brown solid. This material was of sufficient purity to be used in subsequent experiments but an analytical sample was prepared by purification via flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained, which exhibited the following physical properties: mp 169-172 C; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 6.97 (d, J¼3.0 Hz, 1H), and 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.3, 159.9, 130.7, 127.5, 117.9, 107.8, and 52.5; IR (neat) 1704 and 1663 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_7H_7BrNO_3$ 231.9609, found 231.9609.

4-(1-Benzenesulfonyl-1H-indol-3-yl)-5-formyl-1H-pyrrole-2carboxylic acid methyl ester (**11**). Into a 20 mL microwave reaction tube containing a stir bar was placed methyl 3-bromo-2-formylpyrrole-5-carboxylate (0.250 g, 1.22 mmol), 1-(phenylsulfonyl)-3-indolylboronic acid pinacol ester (0.468 g, 1.22 mmol), DABCO (0.160 g,1.43 mmol) along with 9 mL of toluene and 3 mL of ethanol. After stirring the resulting mixture for several minutes, dichloro[1,10-bis-(diphenyl-phosphino)ferrocene]palladium(II) dic hloromethane adduct (0.037 g, 0.031 mmol) was added to the microwave reaction tube followed by the addition of 20 drops of water and the tube was capped and sealed with a crimping tool. The reaction mixture was heated in a Biotage Initiator microwave system for 2 h at 110 C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with 320 mL of ethyl acetate and the combined organic materials were concentrated in vacuo to give a dark solid (0.598 g). The solid was subjected to flash chromatographic purification on a Biotage Isolera system with a SNAP 25 g silica column in which case an orange-red solid was obtained (0.374 g, 90% yield). This material exhibited the following physical properties: mp 160-162 C; ^{1}H NMR (acetone-d_6) δ 9.85 (s, 1H), 8.10-8.14 (m, 4H), 7.68-7.73 (m, 2H), 7.62 (t, J=6.3 Hz, 2H), 7.45 (t, J=6.9 Hz, 1H), 7.36 (t, J=6.9 Hz, 1H), 7.20 (s, 1H), and 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 185.0, 165.4, 143.1, 140.3, 139.6, 136.9, 135.2, 134.9, 133.1, 132.2, 130.8, 130.4, 129.3, 129.2, 125.5, 120.9, 120.2, 118.9, and 56.6; IR (neat) 1720 and 1658 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{21}H_{16}N_2NaO_5S$ 431.0678 found 431.0641.

3-(1-Benzenesulfonyl-1H-indol-3-yl)-1H-pyrrole-2,5dicarboxylic acid 5-methyl ester (**12**). Into a 100 mL round bottomed flask equipped with a magnetic stir bar was placed 4-(1-benzenesulfonyl-1H-indol-3-yl)-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (0.120g, 0.376 mmol) along with 35 mL of DMSO. The flask was placed in an ice bath and sodium dihydrogen phosphate (0.204 g, 2.25 mmol), which had been dissolved in 10 mL of water, was added followed by the dropwise addition of sodium chlorite (0.080 g, 0.881 mmol) in 10 mL of water. The mixture was allowed to stir overnight. The same reaction conditions were repeated exactly for a second time and both reaction mixtures were combined and worked up together. The combined reaction mixtures were adjusted to pH 2 with 6 M hydrochloric acid and then diluted with 200 mL of water and then extracted with ethyl acetate (3x25 mL). The combined organic phases were extracted with brine (2x50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield 0.270g (93% yield) of a yellow solid. This material was of sufficient purity to be used in subsequent experiments but an analytical sample was prepared by purification via flash chromatography on a Biotage Isolera system in which case the resulting solid exhibited the

following physical properties: mp 205-207 C; ^{1}H NMR (acetone-d_6) δ 8.19 (s,1H), 8.03-8.06 (m, 3H), 7.67 (d, J=7.8 Hz,1H), 7.52-7.59 (m, 3H), 7.34 (t, J=7.8 Hz,1H), 7.30 (t, J=7.8 Hz, 1H), 7.14 (s, 1H), and 3.88 (s, 3H); ^{13}C NMR (acetone-d_6) δ 160.2, 138.0, 134.8, 134.1, 130.7, 129.5, 127.0, 126.4, 124.5, 124.4, 123.5, 120.6, 120.4, 116.2, 116.1, 113.5, and 51.1; IR (neat) 1717 and 1677 cm^1; HRMS (ES, M+Na) m/z calcd for $C_{21}H_{16}N_2NaO_6S$ 447.0627 found 447.0605.

3-(1-Benzenesulfonyl-1H-indol-3-yl)-1H-pyrrole-2,5dicarboxylic acid dimethyl ester (**13**). Into a 100 mL round bottomed flask equipped with a magnetic stir bar, reflux condenser, heating mantel and under a nitrogen atmosphere was placed carbonyl diimidazole (0.077 g, 0.470 mmol) and 3-(1-benzenesulfonyl-1H-indol-3-yl)-1H-pyrrole-2,5-dicarboxylic acid 5-methyl ester (0.200 g, 0.470 mmol) in 2 mL of DMF. The reaction mixture was stirred at 40 C for 1 h. Methanol (0.003 mL, 0.94 mmol) was then added to the reaction mixture and the subsequent mixture was maintained at 40°C for 24 h. After the reaction mixture had cooled to room temperature it was diluted with ethyl acetate (20 mL) and the resulting solution was extracted with 10% hydrochloric acid (1x20 mL), saturated aqueous bicarbonate (1x20 mL) and water (1x20 mL). The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield a light yellow solid (0.180 g, 87% yield). This material was of sufficient purity to be used in subsequent experiments but an analytical sample was prepared by purification via flash chromatography on a Biotage Isolera system in which case the resulting solid exhibited the following physical properties: mp 130-132 C; ^{1}H NMR (acetone-d_6) δ 8.06-8.09 (m, 4H), 7.68 (t, J=7.2 Hz, 1H), 7.61-7.64 (m, 3H), 7.40 (t, J=7.8 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.14 (s, 1H), 3.88 (s, 3H), and 3.77 (s, 3H); ^{13}C NMR (acetone-d_6) δ 160.2, 160.8, 138.1, 134.8, 134.2, 130.5, 129.5, 126.9, 126.1, 125.6, 124.7, 123.6, 122.8, 121.5, 120.5, 116.3, 115.7, 113.5, 51.2, and 51.0; IR (neat) 1695 cm^1; HRMS (ES, M+Na) m/z calcd for $C_{22}H_{18}N_2NaO_6S$ 461.0783 found 461.0777.

3-(1-Benzenesulfonyl-1H-indol-3-yl)-4-bromo-1H-pyrrole 2,5-dicarboxylic acid dimethyl ester (**14**). Into a 100 mL round bottomed flask equipped with a magnetic stir bar was placed 3-(1benzenesulfonyl-1H-indol-3-yl)-1H-pyrrole-2,5-dicarboxylic acid dimethyl ester (0.090 g, 0.205 mmol), KOH (0.023 g, 0.410 mmol) and 10 mL of DMF. The resulting mixture was stirred for 15 min and N-bromosuccinimide (0.037 g, 0.205 mmol) was added in one portion. The flask was covered with aluminum foil and the reaction mixture was stirred overnight at room temperature. The reaction was subsequently worked up by dilution with water (20 mL) and a 10% aqueous solution of sodium thiosulfate (20 mL) followed by extraction with ethyl acetate (3x15 mL). The combined organic phases were washed with water (120 mL), brine (115 mL) and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the organic phase was concentrated in vacuo to yield a light yellow solid (0.086 mg, 81% yield). This material exhibited the following physical properties: mp 182-184 C; ^{1}H NMR (acetone-d_6) δ 8.04-8.08 (m, 3H), 7.79 (s, 1H), 7.69 (t, J=7.8 Hz, 1H), 7.62 (t, J=7.8 Hz, 2H), 7.37 (t, J=6.9 Hz, 1H), 7.32 (d, J=6.9 Hz, 1H), 7.28 (t, J=6.9 Hz, 1H), 3.91 (s, 3H), and 3.56 (s, 3H); ^{13}C NMR (acetone-d_6) δ 159.3, 159.1, 138.1, 134.8, 134.2, 130.7, 129.5, 126.9, 126.6, 124.6,123.9, 123.3,

123.2,122.0, 121.0, 115.0, 113.5, 105.7, 51.3, and 51.1; IR (neat) 1699 cm^{1}; HRMS (ES, M+Na) m/z calcd for $C_{22}H_{17}BrN_2NaO_6S$ 538.9888 found 538.9895.

3,4-Bis-(1-benzenesulfonyl-1H-indol-3-yl)-1H-pyrrole-2,5 dicarboxylic acid dimethyl ester (**15**). Into a 20 mL microwave reaction tube containing a stir bar was placed 3-(1-benzenesulfonyl-1H-indol-3-yl)-4-bromo-1H-pyrrole-2,5-dicarboxylic acid dimethyl ester (0.100 g, 0.190 mmol), 1-(phenylsulfonyl)-3indolylboronic acid pinacol ester (0.145 g, 0.380 mmol), and DABCO (0.031 g, 0.270 mmol) along with 9 mL of toluene and 3 mL of ethanol. After stirring the resulting mixture for several minutes, dichloro[1,10-bis-(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.007 g, 0.009 mmol) was added to the microwave reaction tube followed by the addition of 20 drops of water and the tube was capped and sealed with a crimping tool. The reaction mixture was then heated in a Biotage Initiator microwave system for 2 h at 110 C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with ethyl acetate (2x20 mL) and the combined organic phases were concentrated in vacuo to yield a yellow-orange solid (0.210 g). This material was purified via flash chromatography on a Biotage Isolera system in which case a yellow-orange solid (0.082 g, 63% yield) resulted. This material exhibited spectral properties identical with those reported by Gribble and co-workers for bis-N-Benzenesulfonyllycogarubin C: mp 204-206 C (lit. 205-207 C); ^{1}H NMR (acetone-d_6) δ 7.85 (d, J=8.1 Hz, 2H), 7.66-7.71 (m, 6H), 7.58 (t, J=7.5 Hz, 2H), 7.46 (t, J=7.5 Hz, 4H), 7.16-7.24 (m, 4H), 7.01 (t, J=7.5 Hz, 2H), and 3.56 (s, 6H); ^{13}C NMR (acetone-d_6) δ 160.0, 138.0, 134.3, 134.0, 131.0, 129.5, 126.4,126.2,124.4,123.8,123.1,121.7,120.5,115.5,113.1, and 50.9; IR (neat) 1701 cm1; HRMS (ES, M+Na) m/z calcd for $C_{36}H_{27}N_3NaO_8S_2$ 716.1137 found 716.1129.

4-(1-Benzenesulfonyl-1H-indol-3-yl)-3-bromo-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (**17**). Into a 100 mL round bottomed flask equipped with a magnetic stir bar was placed 4-(1benzenesulfonyl-1H-indol-3-yl)-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (0.100 g, 0.245 mmol), KOH (0.014 g, 0.245 mmol) and 10 mL of DMF. The resulting mixture was stirred for 45 min and N-bromosuccinimide (0.087 g, 0.45 mmol), which had been dissolved in 5 mL of DMF, was added in one portion. The flask was covered with aluminum foil and the reaction mixture was stirred overnight at room temperature. The reaction was subsequently worked up by dilution with water (40 mL) and a 10% aqueous solution of sodium thiosulfate (20 mL) followed by extraction with ethyl acetate (3x15 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the organic phase was concentrated in vacuo to yield a solid (0.340 g). This material was purified via flash chromatography on a Biotage Isolera system in which case a white solid (0.105 g, 89% yield) resulted. This material exhibited the following physical properties: mp 211-213 C; ^{1}H NMR (acetone-d_6) δ 9.57 (1H), 8.10-8.12 (m, 3H), 8.02 (s, 1H), 7.71 (t, J=7.2 Hz, 1H), 7.63 (t, J=7.2 Hz, 2H), 7.40-7.48 (m, 2H), 7.31 (t, J=8.7 Hz, 1H), and 3.92 (s, 3H); ^{13}C NMR (acetone-d_6) δ 179.7, 158.3, 137.7, 134.9, 134.5, 131.5, 130.4, 129.7, 129.6, 127.1, 127.0,

125.2, 125.1, 125.0, 123.8, 121.0, 113.6, 113.0, and 51.5; IR (neat) 1713 1672 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{21}H_{15}N_2NaO_5SBr$ 508.9777 found 508.9729.

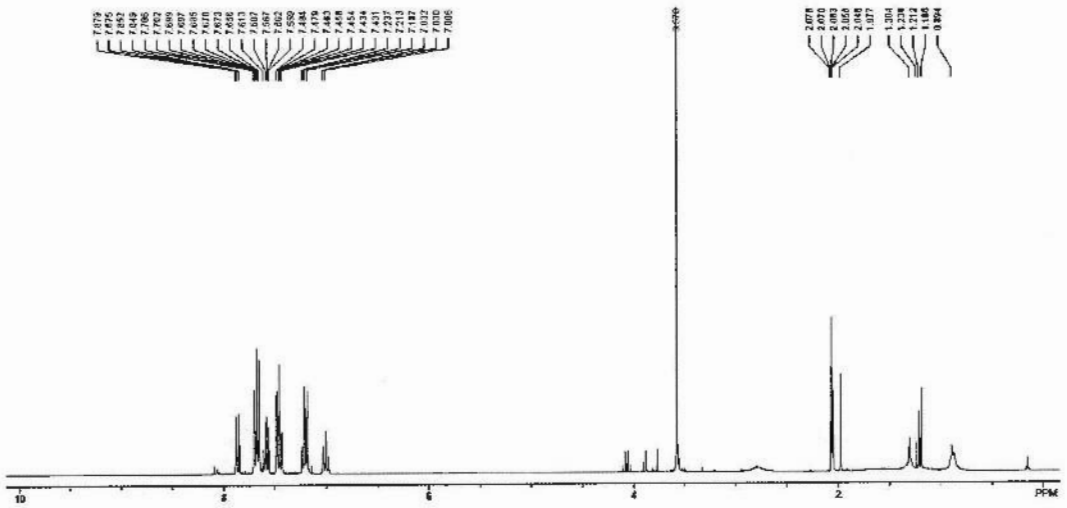
4-(1-Benzenesulfonyl-1H-indol-3-yl)-5-formyl-3-(4-methoxyphenyl)-1H-pyrrole-2-carboxylic acid methyl ester (**18a**). Into a 20 mL microwave reaction tube containing a stir bar was placed 4(1-benzenesulfonyl-1H-indol-3-yl)-3-bromo-5-formyl-1H-pyrrole-2-carboxylic acid ethyl ester (0.080 g, 0.164 mmol), 4-methoxyphenylboronic acid (0.030 g, 0.197 mmol), DABCO (0.026 g, 0.230 mmol), dichloro[1,10-bis-(diphenyl-phosphino)ferrocene]palladium(II) dichloromethane adduct (0.006 g, 0.008 mmol), toluene (9 mL), methanol (3 mL), and water (5 drops). The resulting mixture was stirred and heated in a Biotage Initiator microwave system for 2 h at 110 C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with ethyl acetate (25 mL) and the combined organic phases were concentrated in vacuo to yield an orange solid. The crude product was purified via flash chromatography on a Biotage Isolera system in which case a yellow-orange solid (0.081 g, 96% yield) was obtained and exhibited the following physical properties: mp 75-78 C; ^1H NMR (acetone-d_6) d 9.61 (s, 1H), 7.98 (d, J=6.0 Hz, 1H), 7.90 (d, J=8.4 Hz, 2H), 7.75 (s, 1H), 7.72 (t, J=7.5 Hz, 1H), 7.59 (t, J=6.9 Hz, 2H), 7.28 (t, J=8.1 Hz, 1H), 7.07-7.16 (m, 4H), 6.68 (d, J=8.7 Hz, 2H), 3.77 (s, 3H), and 3.74 (s, 3H); ^{13}C NMR (acetone-d_6) δ 180.5, 160.4, 158.8, 137.7, 134.8,134.3,131.4,131.3, 131.0, 129.7, 129.6, 127.0, 126.8, 126.7, 125.0, 124.5, 123.9, 123.6, 120.5, 114.6, 113.4, 112.8, 54.5, and 51.1; IR (neat) 1714 and 1666 cm^{-1}; HRMS (ES,M+Na) m/z calcd for $C_{28}H_{22}N_2NaO_6S$ 537.1091 found 537.1054.

4-(1-Benzenesulfonyl-1H-indol-3-yl)-5-formyl-3-(3,4,5trimethoxyphenyl)-1H-pyrrole-2-carboxylic acid methyl ester (**18b**). Into a 20 mL microwave reaction tube containing a stir bar was placed 4-(1-benzenesulfonyl-1H-indol-3-yl)-3-bromo-5formyl-1H-pyrrole-2-carboxylic acid ethyl ester (0.150 g, 0.307 mmol), 3,4,5 trimethoxyphenylboronic acid (0.080 g, 0.369 mmol), DABCO (0.048 g, 0.430 mmol), dichloro[1,10-bis(diphenyl-phosphino)ferrocene]palladium(II) dichloro-methane adduct (0.011 g, 0.015 mmol), toluene (9 mL), methanol (3 mL), and water (5 drops). The resulting mixture was stirred and heated in a Biotage Initiator microwave system for 2 h at 110 C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with ethyl acetate (25 mL) and the combined organic phases were concentrated in vacuo to yield a solid. The crude product was purified via flash chromatography on a Biotage Isolera system in which case 0.161 g (91% yield) of an orange solid was obtained and exhibited the following properties: mp 71-74 C; ^1H NMR (acetone-d_6) δ 9.66 (s, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.93 (d, J=7.2 Hz, 2H), 7.84 (s, 1H), 7.71 (t, J=7.5 Hz, 1H), 7.60 (t, J=7.2 Hz, 2H), 7.30 (t, J=8.4 Hz, 1H), 7.07-7.14 (m, 2H), 6.55 (s, 2H), 3.81 (s, 3H), 3.67 (s, 3H), and 3.39 (s, 6H); ^{13}C NMR (acetone-d_6) δ 180.2, 160.4, 152,5, 137.6, 134.5, 131.3, 131.1, 130.9, 129.7, 128.1, 126.8, 126.6, 124.9, 124.1, 123.9, 123.5, 120.6, 114.2, 113.2, 108.3, 93.0, 59.7, 55.3, and 51.3; IR (neat) 1714 and 1666 cm^{-1}; HRMS (ES, M+Na) m/z calcd for $C_{30}H_{26}N_2NaO_8S$ 597.1302 found 597.1237.

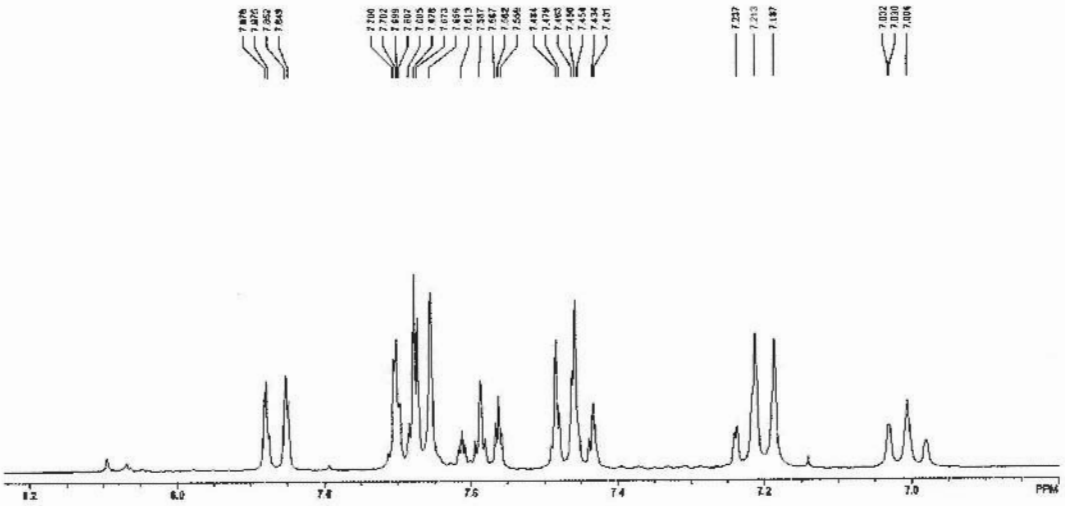
4-(1-Benzenesulfonyl-1H-indol-3-yl)-3-(3,4-dimethoxyphenyl)-5-formyl-1H-pyrrole-2-carboxylic acid methyl ester (**18c**). Into a 20 mL microwave reaction tube containing a stir bar was placed 4(1-benzenesulfonyl-1H-indol-3-yl)-3-bromo-5-formyl-1H-pyrrole2-

carboxylic acid ethyl ester (0.100 g, 0.205 mmol), 3,4-dimethoxyphenylboronic acid (0.045 g, 0.246 mmol), DABCO (0.032 g, 0.287 mmol), dichloro[1,10-bis-(diphenyl-phosphino)ferrocene]palladium(II) dichloro-methane adduct (0.008 g, 0.010 mmol), toluene (9 mL), methanol (3 mL) and water (5 drops). The resulting mixture was stirred and heated in a Biotage Initiator microwave system for 2 h at 110 C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with ethyl acetate (25 mL) and the combined organic phases were concentrated in vacuo to yield a solid. The crude product was purified via flash chromatography on a Biotage Isolera system in which case 0.043 g (39% yield) of a red solid was obtained and exhibited the following properties: mp 68-71 C; ^{1}H NMR (acetone-d_6) δ 9.60 (s, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.90 (d, J=8.4 Hz, 2H), 7.78 (s, 1H), 7.72 (t, J=7.8 Hz, 1H), 7.59 (t, J=7.2 Hz, 2H), 7.30 (t, J=8.4 Hz, 1H), 7.17 (d, J=8.7 Hz, 1H), 7.13 (t, J=8.1 Hz, 1H), 6.70-6.80 (m, 3H), 3.78 (s, 3H), 3.76 (s, 3H), and 3.35 (s, 3H); ^{13}C NMR (acetone-d_6) δ 180.1, 160.4, 148.6, 148.3, 137.7, 134.6, 134.3, 131.3, 131.0, 129.6, 126.7, 126.6, 125.3, 124.9, 124.2, 123.9, 123.6, 122.9, 120.6, 114.5, 114.4, 113.3, 110.8, 55.0, 54.5, and 51.1; IR (neat) 1708 and 1663 cm^{1}; HRMS (ES, M+Na) m/z calcd for $C_{29}H_{24}N_2O_7S$ 567.1196 found 567.1135.

VI. Appendix:



NMR spectrum of 15, lycogarubin C Gribble precursor.



NMR spectrum, closeup of aromatic region of 15, lycogarubin C Gribble precursor.

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